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Datasheet for the decision of 19 October 2006

Case Number: T 0346/05 - 3.3.08

Application Number: 94929221.3

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Title of invention:
Recombinant alphavirus vectors

Patentee:
CHIRON CORPORATION

Opponent:
Bioption AB

Headword:
Alphavirus/CHIRON

Relevant legal provisions:
EPC Art. 56

Keyword:
"Admissibility of documents filed with the statement of grounds of appeal (no)"
"Inventive step of the main and the auxiliary requests (no)"

Decisions cited:
T 0950/99

Catchword:
-

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Case Number: T 0346/05 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 19 October 2006

Appellant: (Opponent)	Bioption AB Hästhagsvägen 30 A S-19163 SOLLENTUNA (SE)
Representative:	Agvald-Glas, Kerstin Gunilla Zacco Sweden AB Box 23101 S-104 35 Stockholm (SE)
Respondent: (Patent Proprietor)	CHIRON CORPORATION 4560 Horton Street Emeryville, California 94608 (US)
Representative:	Hallybone, Huw George Carpmaels and Ransford 43 Bloomsbury Square London WC1A 2RA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 9 December 2004 concerning maintenance of the European patent No. 0694070 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

I. The opponent (appellant) lodged an appeal against the interlocutory decision of the opposition division dated 9 December 2004, whereby European patent No. 0 694 070, which had been granted on European application No. 94 929 221.3 published under the International Publication No. WO 95/07994, was maintained in an amended form on the basis of the main request filed with a letter dated 22 January 2004. The opposition division, which did not admit into the proceedings either the late-filed document D18 (see Section VIII, *infra*) or two other new documents, decided that this request fulfilled the requirements of the EPC. In particular, it was inventive over the closest prior art document D1 (see Section VIII, *infra*).

II. The patent had been opposed on the grounds as set forth in Articles 100(a), (b) and (c) EPC that (i) the invention was neither new (Article 54 EPC) nor inventive (Article 56 EPC), (ii) the invention was not sufficiently disclosed (Article 83 EPC) and (iii) the patent contained subject-matter which extended beyond the content of the application as filed (Article 123(2) EPC). Neither of the added matter or novelty objections was pursued further against the main request on file.

III. On 24 April 2005, the appellant filed a statement setting out the grounds of appeal. Thirteen new documents, numbered as documents D18 to D30, were submitted therewith. The appellant objected to the claim request allowed by the opposition division for reasons of lack of novelty, lack of inventive step and insufficiency of the disclosure. In its view, claims 1

and 3 were not novel in view of document D22. The claim request as a whole lacked inventive step in view of document D1 taken as the closest state of the art in combination with a number of other documents. The appellant also referred to four meetings at which Dr. Peter Liljeström had made presentations on SFV vectors.

IV. On 8 September 2005, the proprietor (respondent) indicated in its reply to the statement setting out the grounds of appeal that the claim request on the basis of which the patent had been maintained by the Opposition Division remained its main request and filed a first auxiliary request. The respondent submitted that lack of novelty did not fall within the legal framework of the appeal for the reason that the appellant had announced at the oral proceedings held before the opposition division that it did not pursue its allegation of lack of novelty.

V. The Board issued a communication under Article 11(1) of the Rules of Proceeding of the Boards of Appeal expressing provisional and non-binding opinions. In reply to this communication, the respondent filed, with a letter dated 18 September 2006, observations which were accompanied *inter alia* by a second auxiliary request and a declaration by Dr Tang (document A in these proceedings; see Section VIII, *infra*), while the appellant filed, with a letter dated 19 September 2006, a document containing both a declaration and a certificate by the Swedish Research Council (document B in these proceedings; see Section VIII, *infra*).

VI. Oral proceedings took place on 19 October 2006. As announced in its letter of 16 October 2006, the appellant did not attend.

VII. Claim 1 of the **main request** (claims as maintained by the opposition division) read:

"1. An alphavirus cDNA vector construct comprising a 5' promoter which is capable of initiating the synthesis of viral RNA in vitro from cDNA, a 5' sequence which is capable of initiating transcription of alphavirus RNA, a nucleotide sequence encoding alphavirus non-structural proteins, an active viral junction region or a modification thereof which retains a functional promoter sequence, wherein said modification results in the inhibition or reduction of viral transcription from the junction region, a heterologous nucleotide sequence and an alphavirus RNA polymerase recognition sequence, wherein said heterologous nucleotide sequence encodes a palliative which is **a gene product which converts a compound with little or no cytotoxicity into a toxic product or** a lymphokine."

(emphasis in bold added by the Board to show the terms which do not appear in the second auxiliary request as indicated below)

Claim 1 of the **first auxiliary request** (filed on 8 September 2005) was identical to claim 1 of the main request.

Claim 1 of the **second auxiliary request** (filed on 18 September 2006) differed from claim 1 of the main

request only in that the terms "*a gene product which converts a compound with little or no cytotoxicity into a toxic product or*" had been deleted, the palliative thus being only a lymphokine.

VIII. The following documents are referred to in the present decision:

(D1) WO 92/10578 (published on 25 June 1992)

(D6) Peter Liljeström and Henrik Garoff, Bio/Technology, Vol. 9, December 1991, Pages 1356 to 1361

(D7) US 5,217,879 (published on 8 June 1993)

(D8) Affidavit of Dr John M. Polo of 3 November 1998

(D9) One page internal document filed with the respondent's letter of 17 November 1999 during the examination proceedings concerning human IL-2 production by transduced tumour cells

(D10) One page internal document filed with the respondent's letter of 22 January 2004 during the opposition proceedings concerning the anti-tumour efficacy of SIN replicon particles

(D13) Peter Liljeström, Current Opinion in Therapeutic Patents, March/April 1993, Pages 375 to 402

(D18) Kenneth W. Culver and R. Michael Blaese, TIG, Vol. 10, No. 5, May 1994, Pages 174 to 178

(D19) Andres A. Gutierrez et al., The Lancet, Vol. 339, 21 March 1992, Pages 715 to 721

(D20) Kenneth W. Culver et al., Science, Vol. 256, 12 June 1992, Pages 1550 to 1552

(D21) Jerzy Trojan et al., Science, Vol. 259, 1 January 1993, Pages 94 to 97

D22) Peter Liljeström, Research Proposal, MFR 1994, 010515, 13 pages, accompanied by an application form from the "Medicinska Forskningsrådet" with registration number P889

(D23) Peter Liljeström, Research Proposal, WHO/UNDP Programme, 02/94

(D24) Ian A. Ramshaw et al., TIBTECH, Vol. 10, December 1992, Pages 424 to 426

(D25) Sondra Schlesinger, TIBTECH, Vol. 11, January 1993, Pages 18 to 22

(D26) Charles M. Rice, Current Opinion in Biotechnology, Vol. 3, 1992, Pages 523 to 532

(D27) Randal J. Kaufman, Current Opinion in Biotechnology, Vol. 3, 1992, Pages 459 to 461

(D28) Bernard Moss, Current Opinion in Biotechnology, Vol. 3, 1992, Pages 518 to 522

(D29) Barrie J. Carter, Current Opinion in Biotechnology, Vol. 3, 1992, Pages 533 to 539

(D30) Priti Tandon Mehrotra et al., The Journal of Immunology, Vol. 151, No. 5, 1 September 1993, Pages 2444 to 2452

(A) Declaration of Dr Tang dated 17 September 2006 submitted with the respondent's letter of 18 September 2006

(B) Declaration/Certificate of the Swedish Research Council filed with the appellant's letter faxed on 19 September 2006

IX. The submissions made in writing by the appellant, insofar as they are relevant to the present decision, may be summarised as follows:

Novelty (Article 54 EPC)

Claims 1 and 3 of the main request lacked novelty over document D22. The declaration/certificate attached to the letter faxed on 19 September 2006 (see document B) established beyond any doubt that document D22 had been made available to the public on 17 January 1994.

Inventive step (Article 56 EPC)

Document D1 was regarded as the closest state of the art. The technical problem to be solved in view of that document was the provision of a means to stimulate the immune system or to stop cells from proliferating, the solution thereto being the expression of a lymphokine from an alphavirus vector. Such an expression was obvious from the teaching of document D1 which

contained an incentive to use the alphavirus vector disclosed therein for gene therapy in combination with in particular document D13. This position was supported by documents D22 and D23 which suggested the use of the Semliki Forest Virus (SFV) expression system to produce cytokines.

X. The submissions made in writing and during the oral proceedings by the respondent, insofar as they are relevant to the present decision, may be summarised as follows:

Admissibility into the proceedings of documents D18 to D30

The opposition division had decided correctly not to admit document D18 into the opposition proceedings for the reason that there was no evidence of publication date/earliest date after the claimed priority date.

Document D22, written by the inventor of the opponent's patent (document D1 in the present proceedings), had also not been admitted into the proceedings before the opposition division. Whereas it was argued to be a novelty destroying document, no credible argument had ever been made as to why that document was not filed at the onset of the opposition proceedings. Furthermore, there was no firm evidence either that document D22 was ever made available to the public or, if so, at what precise date.

Documents D19 to D21 and D23 to D30 had only been filed with the statement setting out the grounds of appeal,

i.e. more than two and half years after the expiry of the opposition period.

Thus, none of these documents should be admitted into the proceedings.

Novelty (Article 54 EPC)

Lack of novelty did not fall within the legal framework of the present appeal since the appellant had withdrawn its allegation of lack of novelty at the oral proceedings held before the opposition division.

Inventive step (Article 56 EPC)

Document D1 generally disclosed the expression system of claim 1 but did not contemplate constructs having, as their heterologous nucleotide sequence, a sequence encoding a palliative which was a gene product converting a compound with little or no cytotoxicity into a toxic product or a lymphokine. Indeed, claim 1 of the main request was directed to a very limited selection of possible heterologous genes, namely genes encoding one of two particular palliatives both involved in gene therapy.

The technical problem to be solved in view of document D1 taken as the closest state of the art was the identification of alternative expression products using its expression system.

Document D1 disclosed the use of alphavirus to transform millions of cells *in vitro* in order to produce large amounts of products. In contrast, it did

not disclose the production of palliatives in an *in vivo* context, i.e. with a view to expressing the gene encoding the palliative in the cells to be treated. There was no contemplation in document D1 of using a nucleotide sequence encoding a palliative useful in gene therapy. Gene therapy was known at the priority date but the idea to use alphavirus only came later. Duration of expression of the gene encoding the palliative was important for gene therapy.

As stated by Dr Polo in his affidavit (document D8), there was nothing inherently obvious in document D1 to teach or even suggest to the skilled person that a strategy similar to the vaccine vector strategy disclosed therein could work for palliatives, such as lymphokines or prodrugs which convert a compound with little or no cytotoxicity into a toxic product. The requirements for successful delivery and use of an alphavirus vector expressing a palliative, with respect to targeting of the appropriate cell type, level of expression and duration of expression, would be expected to be much different than those of vaccine antigen-expressing vectors.

The skilled person could not have predicted with a reasonable expectation of success that the alphavirus vector constructs of document D1 could be utilised to express a gene encoding a palliative in the context of gene therapy.

Documents D9 and D10 reported *bona fide* experiments which showed that there was an advantage in expressing a palliative as in claim 1 of the main request. In particular, document D10 showed how efficient the

expression of interleukin-2 (IL-2) was in a tumour model.

XI. The appellant (opponent) had requested in writing that the decision under appeal be set aside and the European patent be revoked.

XII. The respondent (patentee) requested that the appeal be dismissed or, in the alternative, that the patent be maintained on the basis of the first or the second auxiliary request, filed respectively on 8 September 2005 and 18 September 2006.

Reasons for the Decision

Admissibility of documents D18 to D30

1. Documents D18 to D30 were filed by the appellant together with the statement setting out the grounds of appeal.

2. Although, in principle, an appeal should be based essentially on facts and evidence which were already available to the department of the first instance, parties often rely on additional evidence in their effort to make a full statement of their grounds for revision of the contested decision. Such evidence, although late-filed inasmuch as it is filed after the expiry of the opposition period, is not necessarily refused just for reasons of lateness. Much depends on its *prima facie* relevance, the Board being empowered essentially either to i) to disregard it under Article 114(2) EPC or ii), having admitted it, either

to remit the case to the department of first instance under Article 111(1) EPC for further prosecution or to decide on the case (see decision T 0950/99 of 11 November 2002, point 4 of the reasons).

3. In the present case, the Board, exercising its discretion, decides **not to admit** documents D18 to D30 into the appeal proceedings for the following reasons:

3.1 Document D18 had been already filed with the appellant's letter of 1 November 2004 but was found inadmissible under Article 114(2) EPC by the opposition division at the oral proceedings held before it. This took the view that document D18, a review of strategies for gene therapy, was a document published only in May 1994 from which *prima facie* no relevant information could be derived about the state of the art at the effective filing date of the European patent application 94 929 221.3, i.e. the earliest claimed priority date, namely 15 September 1993 (see point 12 of the decision under appeal). The Board considers that the opposition division correctly exercised its discretion and, therefore, sees no reason to revise the opposition division's decision not to admit document D18 into the proceedings.

3.2 Documents D19 to D21 belong to the state of art. Document D19 is a general review about gene therapy for cancer. Document D20 describes an *in vivo* gene transfer technique using retroviral vector-producer cells for treatment of experimental brain tumours. Document D21 describes the treatment and prevention of rat glioblastoma by immunogenic C6 cells expressing antisense insulin-like growth factor I RNA. In view of

their respective contents, which do not relate to the use of an alphavirus vector for the expression of an heterologous nucleotide sequence, documents D19 to D21 are considered by the Board to be no more relevant than the documents which were already on file before the opposition division, in particular documents D1, D7 and D13 (see points 6 and 7, *infra*).

3.3 Document D22 consists of two parts. The first part is drafted in the form of a scientific article containing a research proposal, the goal of which is to develop vaccines against viral infections using the Semliki Forest virus (SFV) vector system for the expression of virus encoding sequences. The second part is a four page application form of the "Medicinska Forskningsrådet" (the "Scientific Council for Medicine", see document B) signed by Dr Peter Liljeström, the author of the first part. The first page of this form contains a summary of the research proposal made in the first part. The signature is accompanied by a typed date of 15 January 1993 which has been changed in manuscript to 15 January 1994. Document D22 has been relied on by the appellant in the appeal proceedings in support of its objection of lack of novelty, the same document having been found inadmissible at first instance.

3.4 In an attempt to establish that document D22 was made available to the public as from 17 January 1994, the appellant's representative filed by fax on 19 September 2006 a one-page document on the headed notepaper of her own firm containing both a declaration and a certificate, dated 18 September 2006, signed by a "Senior Registry Clerk" of, and bearing the stamp of,

the Swedish Research Council (see document B). The declaration states that the Swedish Research Council is a "state authority" which has existed since January 2001, one of its predecessors being the Scientific Council for Medicine; that, as a "state authority", it complies with certain laws which *inter alia* mean an application to it (for, presumably, research funding) "becomes a public act once it has been registered"; and that "the members of the Research Council's preparation groups will treat the applications confidentially" (emphases added). The certificate states that the original application documents represented by document D22 and handed by Peter Liljeström on 17 January 1994 to the Scientific Council for Medicine "are public acts that have been available to public from the registration date of 17 January 1994".

3.5 The Board is not convinced that the declaration/certificate of 18 September 2006 (document B) provides any reliable evidence, let alone that it establishes beyond doubt, that document D22 was made available to the public either on 17 January 1994 or at all. This follows from, first, the reference to confidential treatment of applications submitted to the Swedish Research Council; second, the uncertain status of the declaration/certificate in document B, it being strange (if not suspicious) that a Senior Clerk of a government agency should, when clearly acting in her capacity as such, make statements as to official practice on the notepaper of a firm of patent attorneys rather than that of the agency itself; and third, the absence in document B of any indication whether or not the legal provisions it refers to applied before January 2001. Therefore, document D22 is not a document

which can be used in support of the appellant's new novelty objection, apart from its highly speculative content which describes only how it was intended to carry out future research.

3.6 Document D23 is equivalent to the first part of document D22 as to its content. It is a research proposal apparently for submission to the WHO/UNDP Programme. No evidence has been provided as to whether, and if so when, the document has been made available to the public and, without such evidence it cannot be used in support of the appellant's inventive step objection, again apart from its highly speculative content.

3.7 Documents D24 to D30 belong to the state of art. Document D24 is a short review focusing on cytokine expression by recombinant vaccinia viruses. D27 is an editorial overview serving the purpose of introducing in one issue of a scientific journal a series of papers including documents D26, D28 and D29 all concentrating on aspects of gene expression in heterologous systems and each reviewing in general terms the use of particular viruses as expression vectors, namely positive-strand RNA viruses such as **alphaviruses** and negative-strand RNA viruses such as the influenza virus (document D26), poxviruses (see document D28), and adeno-associated viruses (document D29). Document D30 describes the effects of interleukin-12 (IL-12) on the generation of cytotoxic activity in human $CD8^+$ T lymphocytes. Like document D26, document D25 concentrates on alphaviruses and their use as gene expression vectors. It contains (see pages 21 to 22) in particular a short paragraph briefly reviewing reports in which the Sindbis virus vector and the Semliki

Forest virus vector have provided a tool for biological research by expressing heterologous genes. In view of their respective contents, which either focus on expression vectors derived from other viruses than alphaviruses (see documents D24 and D27 to D30) or deal briefly with the use of alphaviruses as expression vectors for the expression of an heterologous nucleotide sequence which is not a sequence according to claim 1 (see documents D25 and D26), none of documents D24 to D30 are considered by the Board to be more relevant than those already on file before the opposition division, in particular the prior art documents D1, D7 and D13.

Novelty (Article 54 EPC)

4. As document D22, which has not been admitted into the appeal proceedings, is the only document cited against the novelty of claim 1 of the three requests on file, novelty is not an issue to be discussed in the present decision.

Inventive step (Article 56 EPC)

Main request

5. Claim 1 of the main request is directed to a definite alphavirus cDNA vector construct comprising *inter alia* an active viral junction region or a modification thereof which retains a functional promoter sequence, as well as a heterologous nucleotide sequence encoding a palliative which is a gene product converting a compound with little or no cytotoxicity into a toxic product or a lymphokine.

6. The respondent admitted that alphavirus expression systems using vector constructs according to claim 1, save for the heterogenous gene of choice, were known in the art before the priority date, as illustrated by documents D1 and D7.

6.1 Document D1, which was regarded as the closest state of the art in the decision under appeal, describes alphavirus cDNA vector constructs comprising an isolated natural gene (see page 8, lines 8 and 9) encoding a foreign polypeptide or protein (see page 11, lines 10 to 11). There is no limitation as to the foreign polypeptide or protein, it being noted that Example 7 (see pages 35 to 37) illustrates the heterologous gene expression for genes encoding the cytoplasmic mouse dihydrofolate reductase, the membrane protein human transferrin receptor and the secretory protein chicken lysozyme. The constructs are designed for subsequent expression in an animal host cell. According to one aspect of the disclosure, the foreign polypeptide is a polypeptide antigen for vaccination purpose (see page 14, lines 4 to 6). The respondent has explicitly recognised that, except for the heterologous nucleotide sequence, the constructs of document D1 exactly correspond to those according to claim 1 of the main request.

6.2 Like document D1, document D7 describes alphavirus cDNA vector constructs which contain each and every one of the components of the constructs according to claim 1 which are necessary for the expression of an heterologous nucleotide sequence, i.e. (i) a 5' promoter which is capable of initiating the

synthesis of viral RNA *in vitro* from cDNA (see column 5, lines 33 to 46), (ii) a 5' sequence which is capable of initiating transcription of alphavirus RNA (see the basic intermediate construct Toto 1002 as described in Example 2 in columns 13 to 14), (iii) a nucleotide sequence encoding alphavirus non-structural proteins (see column 15, lines 1 to 59), (iv) a viral junction region (see from line 33 of column 7 to line 2 of column 8 and column 9, lines 23 to 68), and (v) an alphavirus RNA polymerase recognition sequence (see column 6, lines 56 to 68 and column 8, lines 22 to 26). Exemplified are the construction and expression of Sindbis virus clones containing DNA sequences coding for CAT (chloramphenicol acetyltransferase) or tPA (tissue plasminogen activator).

7. Furthermore, the state of the art has recognised that the use of such alphavirus expression systems is generally associated with a number of advantages:

7.1 According to document D1, they allow an extremely high level of protein expression to be obtained (see page 39, lines 4 to 5). This is confirmed in document D6, which appears to be a non-patent literature counterpart of document D1, stating that such systems are highly efficient, easy to use and have a very broad host range (see page 1356, bottom of the right column).

7.2 According to document D7, they are particularly fit for the expression of heterologous nucleotide sequences encoding "therapeutically important proteins" as immunologic growth factors (see column 5, lines 61 to 66).

7.3 According to the review document D13, which refers to the expression systems of document D6 (see point 1 in the Chapter entitled "*Advantages of the alphavirus expression systems*" at the bottom of page 378; citation 26 in document D13 being document D6), extremely high levels of production can be obtained. Moreover, it is stated that "*[I]n addition to their obvious use in basic research and for overproduction of protein, alphaviruses have great potential in immunology and gene therapy*" (emphasis added; see the second paragraph of the section entitled "*Applications*" on page 379).

8. The technical problem to be solved in view of such prior knowledge, e.g. document D1, is regarded as the identification of heterologous nucleotide sequences, other than those being explicitly referred to therein, which could be efficiently expressed, the solution thereto being a construct according to claim 1 of the main request, i.e. a construct comprising a heterologous nucleotide sequence which encodes a palliative which is either a gene product that converts a compound with little or no cytotoxicity into a toxic product or a lymphokine.

9. The question to be answered is whether a skilled person would have found in the state of art an incentive to use as the heterologous nucleotide sequence in the known constructs a nucleotide sequence which encodes such a palliative with a view to producing it upon expression.

10. As lymphokines can have a positive effect on cell growth and direct the immune system response, the skilled person would have certainly realised that

lymphokines such as interleukin-2 (IL-2) are part of the therapeutically important proteins referred to in the parallel document D7 (see point 7.2, *supra*) as "immunologic growth factors".

11. This remark leads the Board to the conclusion that a skilled person facing the technical problem (see point 8 *supra*), being also aware of all the advantages recognised in the state of the art associated with the use of alphavirus expression systems (see point 7, *supra*), would have found a strong incentive in document D7 to use as the heterologous sequence in a construct of document D1 a sequence encoding a lymphokine such as interleukin-2 and would thereby have arrived at one of the constructs of claim 1 without the exercise of inventive skill.

12. The respondent has further argued that the state of the art would not have provided any incentive to the skilled person to prepare constructs according to claim 1 for use in the context of gene therapy.

12.1 In reply to that argument the Board notes that claim 1 does not contain any limitation as to the intended use of the palliative to be produced upon expression of the heterologous nucleotide sequence, let alone any indication that the constructs are for use in gene therapy. Nevertheless, even if such a use were contemplated, the argument is not convincing as the skilled person would have known from the review document D13 that alphavirus expression systems have great potential in gene therapy (see point 7.3, *supra*).

13. The respondent has also argued that, unexpectedly, alphavirus vector constructs are uniquely adapted to provide the "correct" high level expression of lymphokine in tumour cells (see middle of page 6 of its letter dated 8 September 2005).

14. In spite of the vagueness of such statements (it is totally obscure what can be viewed as a "correct" high level of expression), the Board has investigated whether indeed an unexpected result can be derived from the evidence on file, this being either the patent specification itself or the reports in documents D9 and D10, and the declaration of Dr Tang (document A). The Board takes the view that the argument is not convincing for the following reasons:

14.1 The patent does not contain any detailed data in respect of the use of a construct comprising a nucleotide sequence encoding a lymphokine in the context of gene therapy for the treatment of tumours (see paragraph 0077 on pages 9 to 10 in the patent specification, the only point at which such a use is contemplated).

14.2 Document D9 presents information in the form of a histogram indicating a level of human interleukin-2 (IL-2) production by transduced tumour cells measured when using an adenovirus vector, a retrovirus vector and an alphavirus vector. This document only indicates that in undisclosed experimental conditions a particular alphavirus vector comprising, as described in some detail in paragraphs 4 and 5 of the declaration of Dr Tang (document A), an active viral junction region and a nucleotide sequence encoding IL-2 has been

able to produce upon expression in tumour cells 10 000 international units of IL-2 pro 10^6 cells in 24 hours, more than an adenovirus vector and a retrovirus vector the identity of which is not given. There is no indication at all that such a level of expression was efficient in the treatment of the tumour.

14.3 Document D10 presents information in the form of a graph indicating the evolution of the tumour size in a colon carcinoma model upon treatment with sindbis replicon particles expressing IL-2. There is no indication at all in the document of the level of IL-2 expression in the tumour cells.

14.4 The declaration of Dr Tang (document A) does not allow any correlation to be made between documents D9 and D10. Nor the tables attached to that declaration provide any information as to the actual level of IL-2 expression achieved in the tumour cells of the treated CT26 colon carcinoma model.

14.5 Thus, the evidence on file is inappropriate to show anything.

15. Nor is the Board convinced by the further argument of the respondent, made in the affidavit of Dr Polo (document D8) that, based solely upon the disclosure of document D1, one could not determine *a priori* whether the palliative approach, i.e. the use of a construct according to claim 1 in the context of gene therapy, would work without trying, as that declaration puts special emphasis on technical requirements, such as the level of expression and duration of treatment, which

have not been defined at all in the patent or in any of the evidence submitted by the respondent.

16. For these reasons, the Board concludes that a skilled person would have regarded it as obvious to choose as the heterologous nucleotide sequence of a construct according to document D1 one which encodes a lymphokine with a reasonable expectation of success that the nucleotide sequence be efficiently expressed, in particular in the context of gene therapy.

17. For the sake of completeness, the Board would like to stress the point that no data at all have been provided for any constructs according to claim 1 other than those comprising an active viral junction region and a nucleotide sequence encoding a lymphokine. This absence of data prevents any assessment of the possible contribution to the art of such other aspects of the invention of claim 1 and whether any such contribution might have involved an inventive step.

18. Therefore, the constructs of claim 1 of the main request do not involve an inventive step and the main request does not meet the requirements of Article 56 EPC.

Auxiliary requests

19. The same conclusion applies to the first and the second auxiliary requests, as claim 1 of the first auxiliary request is identical to claim 1 of the main request and as claim 1 of the second auxiliary request is directed to those constructs of claim 1 of the main request which comprise either an active viral junction region

or a modification thereof and a nucleotide sequence encoding a lymphokine.

20. As neither the main request nor either of the two auxiliary requests meets the requirements of Article 56 EPC, none of those requests can form a basis for the maintenance of the patent in an amended form. Therefore, in the absence of any other request, the patent should be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar The Chairman

A. Wolinski L. Galligani